Phase 1B Study of the Safety, Tolerance, and Pharmacokinetics of Oral Posaconazole in Immunocompromised Children With Neutropenia

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON39331

Source
ToetsingOnline

Brief title
P03579

Condition

- Other condition
- Leukaemias
- Fungal infectious disorders

Synonym
fungal infection prophylaxis, leukemia, neutropenia

Health condition

stamceltransplantatie patienten

Research involving
Human

Sponsors and support

Primary sponsor: Merck Sharp & Dohme (MSD)
Source(s) of monetary or material Support: Sponsor

Intervention

Keyword: children, neutropenia, pharmacokinetics, posaconazole

Outcome measures

Primary outcome

The primary objective of this study is to evaluate the PK of POS administered orally at three dosage levels to immunocompromised children with neutropenia or expected neutropenia aged 3 months to <18 years.

Secondary outcome

The secondary objective of this study is to evaluate the safety and tolerability of POS administered orally at three dosage levels to immunocompromised children with neutropenia or expected neutropenia aged 3 months to <18 years, and to compare the exposures to POS in pediatric subjects to those from an adult population with similar underlying conditions.

Study description

Background summary

Children who are treated for certain malignancies or for aplastic anaemia or who must undergo a stem cell transplant have an elevated risk of experiencing an invasive fungal infection as a consequence of a combination of factors: frequent and/or long-lasting neutropenia, perforation of the skin and mucosal barrier by catheters and chemotherapy or immunosuppressive therapy and the frequent use of broad-spectrum antibiotics. Prophylaxis against fungal

infection is therefore recommended in such patients, whereby we usually choose an antifungal compound that protects against both Candida as well as Aspergillus. This is currently chiefly being done with itraconazole, which is only well absorbed from the intestines as a drink (Trisporal Oral Solution). We use various compounds (such as fluconazole with Candida and voriconazole with Aspergillus) for infections that break through this prophylaxis. Caspofungin is also available nowadays, with activity against Aspergillus and Candida, as well as (liposomal) amphotericin-B, which has disadvantages in the form of IV administration and nephrotoxicity. Despite this therapeutic armamentarium, we still lose patients to invasive fungal infections and an expansion of the prophylactic and therapeutic possibilities are desired.

Posaconazole (POS) is a new, oral, broad-spectrum antifungal agent. The mechanism of action is selective inhibition of the enzyme lanosterol 14 demethylase (CYP51A1), which is involved in ergosterol biosynthesis in yeasts and moulds. POS has, in comparison to the standard treatments, a better response and shows better survival with refractory aspergillosis in adults. Clinical success has also been obtained with other refractory invasive mould infections which are difficult to treat (including fusariosis, chromoblastomycosis and coccidioidomycosis). POS, in comparison to fluconazole or itraconazole, provides a better prophylaxis against invasive femoral infections and a better survival of neutropenic patients. It also shows, in comparison to FLU, a better prophylaxis and survival in recipients of a Haematopoietic Stem Cell Transplant (HSCT) with Graft Versus Host Disease (GVHD). POS is usually well tolerated by adults and a dose adjustment is not necessary for patients with poor renal function. It has a limited capacity for drug-drug interactions.

POS is authorised for use by adults, among others as prophylaxis and treatment in oncology and stem cell transplant patients, whereby 600 mg (~9 mg/kg/day) and 800 mg per day (~11.5 mg/kg/day) are recommended, respectively.

The present study also includes investigation of the pharmacokinetics of posaconazole in children, whereby no sub-therapeutic dose levels will be used. It is therefore expected that patients exposed to POS will also gain a therapeutic advantage from the treatment. It could certainly be an advantage in patients who have already received prophylaxis for a longer time with a different antifungal compound, because POS can still be active in situations whereby resistance has developed against other antifungal compounds.

A connection between POS efficacy and plasma levels was found in studies with adults and that is why this study is necessary for the selection of a correct dose in children.

Study objective

The primary objective of this study is to evaluate the PK of POS administered

orally at three dosage levels to immunocompromised children with expected neutropenia (selected oncology patients, aplastic anemia patients and patients which undergo a stamcell transplant) aged 3 months to <18 years. The PK-profile will be compared with the data available from adults. The safety and tolerability of POSA will also be evaluated in these children.

Study design

This will be a non-randomized, multicenter, open-label, sequential dose escalation PK study. Subjects enrolled will be immunocompromised children with neutropenia or expected neutropenia between the ages of 3 months to <18 years.

The youngest age group of 3 months to 2 years of age, will not be enrolled until the PK and safety data from the 2 older age groups and first 2 dose groups have been independently reviewed by the Sponsor and the external Data Monitoring Committee. The third dose level will be definitively selected when the data regarding the PK and the safety of the other 2 dose-levels is known.

The administration of posaconazole will take place for a maximum of 28 days, which means that patients will use this rather than the standard antifungal prophylaxis that they would normally receive in the context of their standard treatment. This period is equivalent to the time required for recovery from an intensive chemotherapy cure or a stem cell transplant.

Intervention

Dosing Groups for Age Group 1 (2 years to <7 years) and Age Group 2 (7 years to <18 years)
Group 1: POS oral suspension 12 mg/kg/day orally divided into 2 doses (BID), up to a maximum of 800 mg per day.
Group 2: POS oral suspension 18 mg/kg/day orally divided into 2 doses (BID), up to a maximum of 1200 mg per day.
Group 3: POS oral suspension 18 mg/kg/day orally divided into 3 doses (TID), up to a maximum of 1200 mg per day.

Dosing Groups for Age Group 3 (3 months to <2 years)
Group 1: POS oral suspension 12 mg/kg/day orally divided into 3 doses (TID), up to a maximum of 800 mg per day.
Group 2: POS oral suspension 18 mg/kg/day orally divided into 3 doses (TID), up to a maximum of 1200 mg per day.
There is no planned third dosing group for Age Group 3.

Study burden and risks

Children will receive posaconazole rather than a standard antifungal treatment. Administration will take place as a drink in both cases. The most important

burden consists of the collection of blood samples that will be collected from a central line placed for the standard treatment. The most important disadvantage of that is a mildly elevated risk of a line infection.

POS must preferably be administered with a fat-rich meal. This will not always be possible in children being treated for the underlying condition concerned.

Another potential disadvantage could be that patients must switch antifungal prophylaxis, because the maximum exposure to posaconazole is limited to 28 days. Patients will then again receive the standard prophylaxis, if there is an indication for it.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

1. Children of either sex and of any race, 3 months to <18 years of age.;2. Subjects* parent or legally authorized representative must be willing to give written informed consent. Assent will be obtained from minors according to institutional practices.;3. Subjects must have documented or anticipated neutropenia (ANC <=500/mm3 [0.5 x 109/L]) expected to last for at least 7 days and only in the following clinical situations:
a. Acute leukemia (including new and relapse),
b. Myelodysplasia,
c. Severe aplastic anemia,
d. Autologous HSCT recipients,
e. High risk neuroblastoma,
f. Advanced stage non-Hodgkin*s lymphoma.
g. Recipients of allogeneic HSCT during the pre-engraftment period
(neutropenia period).;4. Male and female subjects of child-bearing potential must agree to use a medically accepted method of contraception throughout the study and for at least 30 days after stopping the medication, unless they are surgically or medically sterile or agree to abstain from sexual intercourse. Acceptable methods of contraception include 2 of the following:
a. Condoms (male or female) with spermicide,
b. Diaphragm or cervical cap (if acceptable according to local standard of care) with spermicide
(females),
c. Hormonal contraceptives or intrauterine device with spermicide (females).

Exclusion criteria

1. Subjects with proven IFI, as defined by the MSG/EORTC criteria (see Appendix 3), prior to study entry.;2. Subjects with Grade 3 or Grade 4 nausea and/or vomiting at Screening.;3. Subjects who have received POS within the past 10 days prior to Screening.;4. Subjects receiving prohibited drugs (please refer to Table3).;5. Subjects whose laboratory tests are outside normal limits, as follows:
a. AST or ALT >5 times the upper limit of normal (ULN)
b. Serum total bilirubin >2.5 x ULN
c. Calculated creatinine clearance <30 mL/min. Creatinine clearance will be calculated using the
following equation: Creatinine clearance = k*height (cm)/serum creatinine (mg/dL)
Where k = 0.45 for a full term baby less than 1 year old; 0.55 for children up to 12 years old; 0.55
for females between the ages of 13 and 21 years; 0.7 for males between the ages of 13 and 21
years.;6. Subjects with QTc prolongation:
a. Symptomatic QTc prolongation >450 msec (males) or >470 msec (females)
b. Any QTc prolongation of >500 msec;7. Subjects who are unable to receive study drug

enterally.;8. Female subjects who are pregnant, intend to become pregnant during the course of the study, or are breast-feeding.;9. Subjects with a history of anaphylaxis attributed to the azole class of antifungal agents.;10. Subjects with any clinically significant condition or situation, other than the condition being studied that, in the opinion of the investigator, would interfere with the study evaluations or optimal participation in the study, including receiving less than 7 days of POS.;11. Subjects who have already participated in this study or are participating in any Phase 1 clinical study or any study for a medication that has not yet received regulatory approval. Note: If the medication has received a regulatory approval for use in adults, then the medication would be considered to have received a regulatory approval for the purpose of this criterion. Any medication received by eligible subjects must also be aligned with the protocol guidance for prohibited medications (Table 3). ;12. Subjects who are part of the study staff personnel or family members of the study staff personnel.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-08-2011
Enrollment:	23
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Noxafil
Generic name:	Posaconazole
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	01-06-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	20-05-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	25-07-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-09-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-09-2011
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-06-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-08-2012
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO	

Date:	12-03-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-03-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-05-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	04-10-2013
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	03-03-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-004645-15-NL
CCMO	NL31381.000.10
Other	zie aanvullende opmerkingen